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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 1980N-0050]

RIN 0910-AA01

Anorectal Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that any over-the-counter (OTC) drug product containing a combination of hydrocortisone and pramoxine hydrochloride (HCl) for anorectal use is not generally recognized as safe and effective and is misbranded. This combination product is not currently marketed OTC. This final rule discusses data on the combination of hydrocortisone and pramoxine HCl that were still under review when an earlier final rule on OTC anorectal drug products was issued. This rule is part of FDA's ongoing review of OTC drug products.

DATES: This rule is effective *[insert date 30 days after date of publication in the Federal Register]*.

FOR FURTHER INFORMATION CONTACT: Michael T. Benson, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2222.

SUPPLEMENTARY INFORMATION:

cd02101

DMB

Display Date 8-22-03
Publication Date 8-25-03
Certifier J. Cooke

NFR 4

I. Background

In the **Federal Register** of May 27, 1980 (45 FR 35576), FDA published an advance notice of proposed rulemaking to establish a monograph for OTC anorectal drug products together with the recommendations of the Advisory Review Panel on OTC Hemorrhoidal Drug Products (the Hemorrhoidal Panel), which was the advisory review panel responsible for evaluating the data on the active ingredients in this class of drugs. The agency's tentative final monograph (TFM) on OTC anorectal drug products was published in the **Federal Register** of August 15, 1988 (53 FR 30756). Hydrocortisone as a single ingredient or in combination with pramoxine HCl was not discussed in the TFM. In response to the TFM, the agency received a submission, containing data, information, analyses, views, legal arguments, and a hearing request, to support monograph status for a combination OTC drug product containing hydrocortisone and pramoxine HCl for use as an anti-inflammatory, antipruritic, anesthetic agent (Ref. 1). The requester asked that: (1) The definition section of the proposed anorectal monograph (§ 346.3 (21 CFR 346.3)) be amended to provide for a drug that has anti-inflammatory properties, such as hydrocortisone, (2) hydrocortisone be allowed to be combined with other appropriate ingredients at OTC strengths, including a topical anesthetic such as pramoxine HCl and, (3) a combination of hydrocortisone 0.5 percent and 1 percent pramoxine HCl be generally recognized as safe and effective.

When the OTC anorectal drug products final monograph was published on August 3, 1990 (55 FR 31776 at 31779), the hearing request relating to hydrocortisone individually and in combination had not been evaluated and, therefore, was not addressed in that document. After publication of the final rule, the agency responded to the submission (Ref. 1) and stated that: (1) It

does not provide sufficient evidence to demonstrate that each of the active ingredients in the combination product contributes to the claimed effects and (2) it has not been shown that the combination is generally recognized as safe and effective, whether under the TFM for OTC external analgesic drug products (48 FR 5852, February 8, 1983), the TFM or FM for OTC anorectal drug products, current regulations, or the agency's OTC combination drug product guidelines. The agency's detailed comments are on file in the Division of Dockets Management (Ref. 2).

Subsequently, the requester submitted additional information (Ref. 3). In this final rule, the agency responds to the additional information and includes the combination of hydrocortisone with pramoxine HCl as a nonmonograph (not generally recognized as safe and effective) anorectal drug product in new § 310.545(a)(26)(xi) (21 CFR 310.545(a)(26)(xi)). Any such product marketed OTC would be subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule.

II. The Agency's Final Conclusions on Hydrocortisone Individually and in Combination With Pramoxine HCl for Anorectal Use

The requester contended (Ref. 3) that the proposed combination meets, both from a scientific and legal perspective, the agency's OTC combination drug product policy in that a combination of hydrocortisone (0.25 to 1 percent) and pramoxine HCl 1 percent, is generally recognized as safe and effective for use in OTC drug products to relieve symptoms associated with idiopathic pruritus ani, such as anorectal swelling, pain, itching, and burning. The requester asked the agency to amend the OTC external analgesic drug products TFM and the anorectal drug products FM to include an external analgesic-

anorectal OTC drug product containing the active ingredients hydrocortisone and pramoxine HCl. In the alternative, the requester asked for an oral hearing.

The requester's arguments and the agency's responses follow:

(Comment 1) Hydrocortisone is a proposed Category I ingredient and; therefore, FDA considers it safe and effective for OTC use. The ingredient is included in the OTC external analgesic drug products TFM (55 FR 6932 at 6951, February 27, 1990). FDA considers hydrocortisone safe and effective to relieve swelling and itching associated with various skin conditions, including anal itching (55 FR 6932 at 6933).

(Agency response) The agency agrees that hydrocortisone as a single ingredient is safe and effective for OTC use for the claims proposed in § 348.50(b) (21 CFR 348.50(b)) (55 FR 6932 at 6951). However, data are lacking to support any combination drug products containing hydrocortisone with other OTC drug active ingredients. Further, the 1990 TFM cited by the requester did not include the term "swelling" as an acceptable claim.

(Comment 2) Pramoxine HCl is a Category I ingredient, and thus FDA considers it safe and effective for OTC use. The ingredient is included in § 346.10(g) (21 CFR 346.10(g)) of the OTC anorectal drug products FM for the treatment of various anorectal conditions, including pain, burning, itching, discomfort, and/or irritation. The requester contended that OTC anorectal drug products containing pramoxine HCl in the established dosages of 0.5 to 1 percent that are indicated to relieve pruritus and may be lawfully marketed in accordance with the OTC anorectal drug products FM.

(Agency response) Pramoxine HCl 0.5 to 1 percent is a proposed Category I ingredient as a local anesthetic in the TFM for OTC external analgesic drug products (48 FR 5852 at 5867). The requester mentioned that this concentration

range could be used in OTC anorectal drug products. However, only a 1 percent concentration is included in § 346.10(g) of the OTC anorectal drug products monograph as this was the only concentration evaluated in that rulemaking. The agency lacks data to support a lower concentration for external anorectal use.

(Comment 3) The agency has the authority to switch the status of a product from prescription to OTC when the active ingredient or the combination of active ingredients is determined to be safe and effective for OTC use. The requester cited the **Federal Register** of August 4, 1976 (41 FR 32580) and May 11, 1972 (37 FR 9464 at 9470) as sources for that authority.

(Agency response) The agency has made the determination that the combination of hydrocortisone and pramoxine HCl is not safe and effective for OTC use. Therefore, switching the status of the product from prescription to OTC is not an option. Although the agency is not bound by the recommendations of its advisory panels, the panels that reviewed these ingredients did not recognize any combination of “amine” and “caine” type local anesthetics with hydrocortisone preparations as safe and effective. The requester has also failed to provide adequate information to support a determination that the combination is safe and effective. The agency lacks sufficient data from available sources to propose a combination of hydrocortisone and pramoxine HCl for OTC use in the applicable OTC drug rulemakings.

(Comment 4) Combination products containing hydrocortisone and pramoxine HCl should have been reconsidered by the agency when it extended the concentration range for hydrocortisone up to 1 percent. Specifically, the agency has the obligation to reconsider combination products when it

determines that all of the active ingredients contained in the combination are Category I, and an interested person has requested the combination be considered under a particular OTC drug rulemaking proceeding (21 CFR § 330.10(a)(7) and (a)(12)) (21 CFR 330.10(a)(7) and (a)(12)).

(Agency response) The agency disagrees. The agency's proposal to increase the maximum concentration of hydrocortisone from 0.5 to 1 percent occurred in the rulemaking for OTC external analgesic drug products based on data on the single ingredient and not on combination products. There were no proposed hydrocortisone combinations in that rulemaking. The data on the combination of hydrocortisone 1 percent and pramoxine HCl were submitted to the rulemaking on OTC anorectal drug products and had not been reviewed by the agency at the time it published the amendment to the OTC external analgesic TFM on February 27, 1990 (55 FR 6932) extending the strength of hydrocortisone up to 1 percent. The agency published the FM on OTC anorectal drug products on August 3, 1990 (55 FR 31776 at 31777), in which it stated that hydrocortisone combinations were under review and the agency's evaluation would be reported separately in the future. Simultaneous publication of the agency's evaluation of the single ingredient hydrocortisone in the rulemaking for OTC external analgesic drug products and hydrocortisone-pramoxine HCl combinations in the rulemaking for OTC anorectal drug products would have delayed publication of the anorectal FM for several years.

(Comment 5) Prior to completing the FM for OTC external analgesic drug products, the agency should conduct a retrospective analysis of previously reviewed (or "should have been reviewed") hydrocortisone combinations marketed before 1979.

(Agency response) The agency previously reviewed combination drug products containing hydrocortisone and pramoxine HCl submitted during the 1970s and 1980s. In a notice of proposal to withdraw approval of abbreviated new drug applications for fixed combination drug products containing hydrocortisone acetate and pramoxine HCl, the agency found no evidence that pramoxine HCl contributed an effect to the combination drug product (53 FR 25013, July 1, 1988).

(Comment 6) The agency has consistently applied its combination policy, except with respect to a hydrocortisone and pramoxine HCl combination. The agency did not require additional data in support of the effectiveness of combinations in the monographs for OTC antacid (simethicone and an antacid), cough-cold (ingredients from different pharmacological groups), laxative (bulk and stimulant laxatives), and anorectal drug products (not requiring final formulation testing of combination products and accepting the combinations as formulated).

(Agency response) The agency has consistently focused on the safety and effectiveness of each active ingredient, the rationale for concurrent therapy, the contribution each ingredient makes to the combination, and the marketing history to support Category I classification of combinations. Marketing history for the products cited by the requester provided more extensive data than were available for a combination of hydrocortisone and pramoxine HCl for anorectal use. There was an extensive marketing history for combinations of an antacid and simethicone, an antiflatulent, ingredients with different indications. The agency required additional data for a number of cough-cold combinations in the TFM for those products (53 FR 30522, August 12, 1988). The combinations in the laxative TFM (50 FR 2124 at 2152 and 2153, January 15, 1985) and

anorectal FM involve ingredients with the same indication. The Advisory Review Panel for OTC Laxative Drug Products (Laxative Panel) looked at laxative combinations and determined that each active ingredient had to make a contribution toward laxation. The Laxative Panel recommended monograph status only for combinations it determined had sufficient data. FDA agreed with the Panel's recommendation, and the agency has requested additional data to support other laxative combinations. The Hemorrhoidal Panel evaluated and recommended combinations of anorectal ingredients (45 FR 35576 at 35673), but did not evaluate hydrocortisone because information on that ingredient was not submitted for its review. The Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (Topical Analgesic Panel) discussed combinations of external analgesic ingredients, including hydrocortisone and pramoxine HCl, but did not recommend this combination for monograph status (44 FR 69768 at 69790, December 4, 1979).

The agency has not always accepted a panel's recommendation that specific combinations should be allowed, without having adequate supporting data. For example, the Advisory Review Panel on OTC Antimicrobial (II) Drug Products recommended monograph status for combinations of up to three antifungal ingredients and hydrocortisone or hydrocortisone acetate 0.5 to 1 percent (47 FR 12480, March 23, 1982). The agency disagreed with that panel's recommendations because the agency found that these combinations lacked adequate evidence of effectiveness (47 FR 12480 at 12481). The rulemaking for antifungal drug products has been completed and, because adequate data were not provided to support this combination, it remains nonmonograph. No combination containing hydrocortisone has been found to be generally

recognized as safe and effective for OTC use. Thus, the agency is consistent in requiring additional data to support this hydrocortisone-pramoxine HCl combination.

(Comment 7) Currently marketed prescription products containing 1 percent or less hydrocortisone and 1 percent pramoxine HCl meet the combination policy implemented by the agency. The OTC drug combination policy standards are satisfied because the active ingredients are Category I, are present in the established dosage range, and each ingredient represents a different therapeutic category. The requester also mentioned a previously submitted clinical protocol (Ref. 3) that was not initiated because this protocol was suspended following a meeting with FDA (Ref. 4).

(Agency response) The agency's requirements for OTC drug combination products in § 330.10(a)(4)(iv) also include that each active ingredient makes a contribution to the product's claimed effect(s). The agency has no data showing that the combination of hydrocortisone and pramoxine HCl has been clinically tested against each individual active ingredient and a placebo. As the agency discussed in its January 13, 1994, letter to the requester (Ref. 2), the submitted data did not include these types of studies. Further, the studies from the literature did not involve a patient population where the product is intended for OTC use, nor were they for the proposed OTC anorectal indication. Therefore, based on the available data, the agency is unable to conclude that each active ingredient makes a contribution to the product's claimed effect(s) and that this combination is generally recognized as safe and effective. After the agency received a letter indicating that the requester's client had suspended an ongoing study of the combination (Ref. 4), the agency was under the impression that there was no longer interest in having the protocol

reviewed. The requester should notify the agency if there is still interest in conducting the appropriate study and having the protocol reviewed.

(Comment 8) The combination of 1 percent or less hydrocortisone and 1 percent pramoxine HCl is warranted because hydrocortisone is a therapeutic equivalent of other active antipruritic ingredients that may be combined with a local anesthetic such as pramoxine HCl. In the past, the agency has permitted active ingredient substitutions with pharmacological classes. Further, while the method of action of hydrocortisone is different than other antipruritic agents, the requester suggests that it can be properly combined with local anesthetics, because it is therapeutically equivalent, if not superior, to other approved antipruritic agents.

(Agency response) The agency's response under section II, comment 6 of this document applies here also. The requester's belief that the combination of an antipruritic/analgesic with a local anesthetic is permitted by implication is incorrect. Section 346.22 (21 CFR 346.22) provides for the combination of an "antipruritic/analgesic and a local anesthetic with an astringent." The ingredients under proposed § 348.10 (48 FR 5852 at 5868) are classified as "analgesic/anesthetic/antipruritic."

Listed combinations of external analgesic active ingredients under proposed § 348.50 include ingredients listed under § 348.10(a), (b), and (c) exclude hydrocortisone preparations which are listed under proposed § 348.10(d)(1) as hydrocortisone and under (d)(2) as hydrocortisone acetate. The Topical Analgesic Panel classified hydrocortisone preparations in a listing of ingredients that depress cutaneous sensory receptors (analgesics, anesthetics, and antipruritics) (44 FR 69768 at 69865, December 4, 1979). The agency subdivided the analgesic, anesthetic antipruritic ingredients into

separate classes, i.e., "caine" type local anesthetics, alcohols and ketones, antihistamines, and hydrocortisone preparations (48 FR 5852 at 5867 and 5868, February 8, 1983). The Topical Analgesic Panel did not have adequate data to consider hydrocortisone and pramoxine HCl interchangeable, and the agency has no basis to recommend their interchangeability and inclusion in any OTC drug product monograph.

(Comment 9) If the agency is unable to conclude from the information presented that the proposed combination is Category I, the agency should grant a hearing in this matter.

(Agency response) The agency has evaluated all of the evidence in support of a combination of hydrocortisone and pramoxine HCl in the administrative record for the rulemaking for OTC anorectal drug products submitted on behalf of the requester's client. The agency has discussed this information in its letter of January 13, 1994 (Ref. 2) and in this document. The agency does not find an oral hearing warranted.

III. Analysis of Impacts

FDA has examined the impacts of this final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts, and equity). Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small

entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation). The final rule that led to the development of this supplemental final rule was published in 1990, before the Unfunded Mandates Reform Act of 1995 was enacted. The agency explains in this final rule that the final rule will not result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million.

The agency concludes that this final rule is consistent with the principles set out in the Executive order and in these two statutes. The final rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. Further, since this final rule makes no mandates on government entities and will result in expenditures less than \$100 million in any one year, FDA need not prepare additional analyses under the Unfunded Mandates Reform Act.

The purpose of this final rule is to establish that OTC anorectal drug products containing a combination of hydrocortisone and pramoxine HCl are not generally recognized as safe and effective. Because no such products are currently marketed OTC, the final rule will not have an economic impact on any entity (no reformulations or relabeling are necessary) and will not require any new reporting or recordkeeping activities.

The agency has no alternative course of action as the data are inadequate to support monograph status for this combination product. Therefore, no additional professional skills are needed. The Commissioner of Food and Drugs

certifies that this final rule will not have a significant economic impact on a substantial number of small entities. No further analysis is required under the Regulatory Flexibility Act (5 U.S.C. 605(b)).

IV. Paperwork Reduction Act of 1995

This final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

V. Environmental Impact

The agency has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VII. References

The following references are on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, in Docket No. 1980N-0050 and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. HER1.
2. LET26.
3. Comment No. C25.
4. OTC vol. 12FR3.

List of Subjects in 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 is amended as follows:

PART 310—NEW DRUGS

■ 1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b-360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b-263n.

■ 2. Section 310.545 is amended by adding paragraph (a)(26)(xi), by revising paragraph (d) introductory text, by revising paragraph (d)(13), and by adding paragraph (d)(37) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(26) * * *

(xi) *Combination drug products.* Any combination drug product containing hydrocortisone and pramoxine hydrochloride.

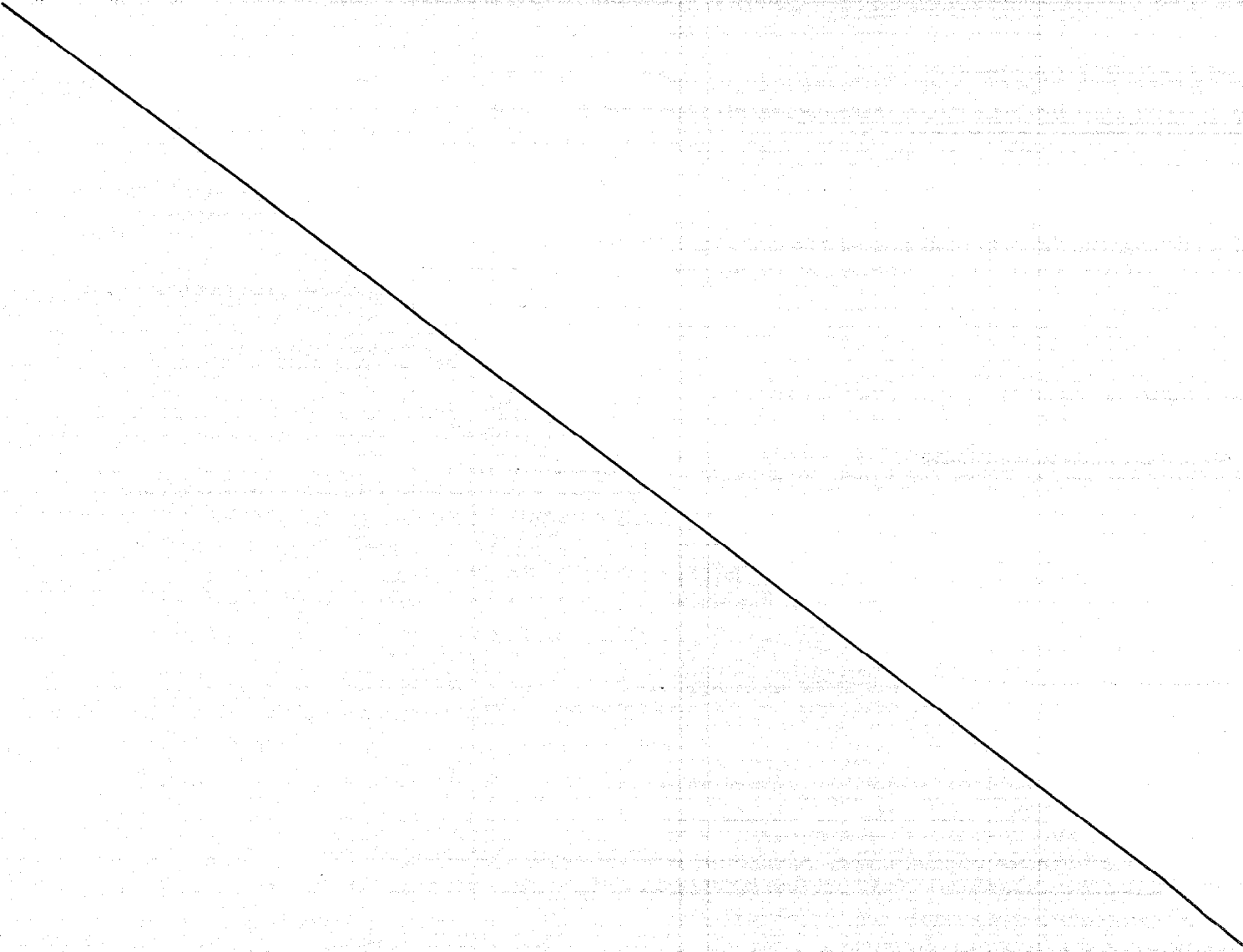
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(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(37) of this section.

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(13) August 5, 1991, for products subject to paragraph (a)(26) of this section, except for those that contain live yeast cell derivative and a combination of hydrocortisone and pramoxine hydrochloride.

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(37) [Insert date 30 days after date of publication in the **Federal Register**],
for products subject to paragraph (a)(26)(xi) of this section.

Dated: _____

8/18/03
August 18, 2003.**CERTIFIED TO BE A TRUE
COPY OF THE ORIGINAL**

Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. 03-????? Filed ??-??-03; 8:45 am]

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